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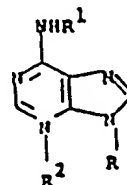
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(54) Purine derivatives and their use
in the defoliation of cotton plants

(57) A novel enantiomer of a purine
derivative having the general formula:



wherein R and R² are hydrogen or alkyl
and R¹ is C₂₋₆ alkyl or α -(C₁₋₄
alkyl)benzyl, or a salt thereof, the
enantiomer being substantially free
from the other enantiomer, is useful
for the defoliation of a growing cotton
plant.

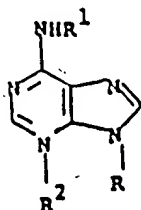
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SPECIFICATION Cotton defoliation

This invention relates to the defoliation of cotton plants.

In the mechanical harvesting of cotton crops, the presence of green leaves and stems on the cotton plants is disadvantageous, since the leaves and stems tend to be crushed during the harvesting operation, and to leave green stains on the cotton. Accordingly it is general practice to spray the crop, at a convenient interval before harvesting, with a chemical which is capable of defoliating the cotton plants.

Purine derivatives of general formula (I):—



10

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wherein R is hydrogen or C₁₋₄ alkyl, R¹ is C₂₋₆, for example C₂₋₄, alkyl wherein the carbon atom adjacent to the nitrogen atom is an asymmetric carbon atom or R¹ is α-(C₁₋₄ alkyl)benzyl optionally ring substituted with 1, 2 or 3 substituents selected from the class consisting of halogen, trifluoromethyl and C₁₋₄ alkoxy, and R² is hydrogen or C₁₋₄ alkyl; or a salt thereof with an acid or base, have cotton defoliating activity.

Each of the purine derivatives contains a chiral centre adjacent to the nitrogen atom in the 6-position (and indeed may contain one or more further chiral centres). Each of the purine derivatives thus can exist in the form of a racemic mixture of two enantiomers. We have found that one of these enantiomers has higher cotton defoliating activity than the other enantiomer. For example, in the case of the purine derivatives of general formula (I) wherein R¹ is α-methylbenzyl, it is the R-enantiomer that has the higher activity.

The invention therefore provides a method of defoliating a growing cotton plant, which method comprises applying to the plant an enantiomer of a purine derivative as defined above, or a salt thereof with an acid or base, the enantiomer applied being substantially free from the other enantiomer of the purine derivative. Suitably the enantiomer applied is associated with less than 10%, preferably less than 5%, by weight of the other enantiomer.

Suitable alkyl and alkoxy groups are methyl, ethyl, propyl (n- or l-propyl), butyl (n-, l-, sec- or t-butyl), methoxy and ethoxy. The halogen can be fluorine, chlorine, bromine or iodine.

When R¹ is C₂₋₆ alkyl, it is suitably sec-butyl, 1-methylbutyl, 1,3-dimethylbutyl, 1-methylpentyl, 1,4-dimethylpentyl, 1,3-dimethylpentyl, or 1,2,4-trimethylpentyl. It is preferred that the alkyl group is one having 4 or 5 chain carbon atoms and one, two or three methyl substituents on the chain. When R¹ is α-(C₁₋₄ alkyl)benzyl, it can be α-methylbenzyl or α-ethylbenzyl optionally ring substituted with one chlorine, trifluoromethyl or methoxy.

The salts can be with an alkali metal or an alkaline earth metal cation (for example a sodium, potassium, calcium, or magnesium cation), an ammonium cation or a mono-, di-, tri- or tetra-substituted ammonium cation in which the substituents may be, for example, C₁₋₄ alkyl. An example of the latter cations is the tetra-n-butyl ammonium cation. Alternatively the salts can be with an inorganic or organic acid, e.g. hydrochloric, hydrobromic, hydroiodic, nitric, sulphuric, toluenesulphonic, acetic or oxalic acid.

Examples of the racemic purine derivatives of general formula (I), from which the enantiomers are derived, as well as some of the enantiomers themselves, are listed in Table I:—

TABLE I

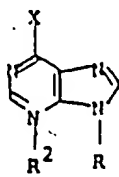
| PURINE NO | R | R ¹ | R ² | MELTING POINT (°C) |
|-----------|----|-------------------------------------------------------------------------------------------|----------------|--------------------|
| 1* | H | C ₆ H ₅ CH(CH ₃)— | H | 196.5–198.5 ° |
| 1A* | H | C ₆ H ₅ CH(CH ₃)— | H | 164.5–166.5 ° |
| 1B* | H | C ₆ H ₅ CH(CH ₃)— | H | 165–166.5 ° |
| 2 | H | C ₂ H ₅ CH(CH ₃)— | H | 159–160 ° |
| 3 | Me | C ₆ H ₅ CH(CH ₃)— | H | 147–148 ° |
| 4 | H | CH ₃ (CH ₂) ₂ CH(CH ₃)— | H | 132–133 ° |
| 5 | Me | CH ₃ (CH ₂) ₂ CH(CH ₃)— | H | 47–48 ° |
| 6 | H | CH ₃ (CH ₂) ₃ CH(CH ₃)— | H | 110–111 ° |
| 7 | H | (CH ₃) ₂ CHCH ₂ CH(CH ₃)— | H | 166–168 ° |
| 8 | H | CH ₃ CH(CH ₃)(CH ₂) ₂ CH(CH ₃)— | H | 92–93 ° |
| 9 | H | CH ₃ CH ₂ CH(CH ₃)CH ₂ CH(CH ₃)— | H | 98–100 ° |
| 10 | H | C ₆ H ₅ CH(CH ₃)— | Me | 39–41 ° |
| 11 | H | C ₆ H ₅ CH(CH ₃)— | H | 59–61 ° |

* Compounds 1A and 1B are enantiomers of each other; Compound 1A is the R-isomer and Compound 1B is the S-isomer. Compound 1 is a mixture of the two isomers.

The following salts of Purine 4 have been prepared: the hydrochloride (Purine 12; m.p. 215—219°) and the hydrobromide (Purine 13; m.p. 244—245°). The tetra-*n*-butyl ammonium salt (Purine 14) of Purine 1 has also been prepared (as an oil).

The invention also provides an enantiomer of a purine derivative of general formula (I) wherein R, R¹ and R² are as defined above, or a salt thereof, the enantiomer being substantially free from the other enantiomer of the purine derivative.

The purine derivative can be prepared by reacting a purine of general formula (II):—



wherein R and R² are as defined above and X is halogen (e.g. chlorine or bromine), or a salt thereof, with an amine of general formula (III):—



wherein R¹ is as defined above, or a salt thereof. If the amine used is an optically active amine, an optically active purine is obtained. If the amine is in the form of an optically pure enantiomer (i.e. it is substantially free from the other enantiomer), an optically pure enantiomer of the purine derivative is obtained. If the amine is in the form of a racemic mixture, the purine is obtained in the form of a racemic mixture. The desired purine enantiomer can be obtained in substantially optically pure form from the racemic mixtures and other enantiomeric mixtures by conventional resolution techniques.

By way of example, when the amine used is *d*- α -methylbenzylamine, the purine obtained is the *R*-enantiomer of 6-(α -methylbenzylamino) purine (i.e. Purine 2A).

When the amine is a low boiling amine, the reaction can for example be performed as follows. The purine of general formula (II) is refluxed with a large excess of the amine. When the reaction is complete, the excess amine is removed by distillation under reduced pressure. The residue is then dissolved in an inert water-immiscible organic solvent and the solution washed with water to remove the amine hydrochloride formed as a by-product. The solution is then dried and concentrated to give the crude product which is recrystallised from a suitable solvent. When the amine is a high boiling amine, the same procedure can be used except that a smaller excess of the amine is used and the reaction mixture is diluted with a lower alcohol (e.g. ethanol or butanol).

The resolution of the racemic and other enantiomeric mixtures can, as indicated above, be performed by known methods, for example forming the diastereoisomeric salts or derivatives (e.g. amides) of the enantiomeric mixtures by reaction with an optically active acid or derivative thereof, separating the diastereoisomeric salts or derivatives by, for example, crystallisation techniques, and converting the separated isomeric salts or derivatives into the required enantiomer.

The cotton defoliant may, if desired, be applied in admixture with herbicides, desiccating agents and/or other defoliating agents.

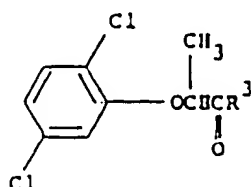
Suitable herbicides are salts of the bipyridylum herbicides, paraquat and diquat. Paraquat and diquat are the accepted common names for the 1,1'-dimethyl-4,4'-bipyridylum cation and the 1,1'-ethylene-2,2'-bipyridylum cation, respectively.

The particular salt of paraquat or diquat used is not critical. Conveniently the salt is one which is readily soluble in water.

Examples of suitable paraquat salts are the chloride, bromide, iodide, methylsulphate, sulphate, methylphosphate, and phosphate, while examples of diquat salts are the chloride, bromide, iodide, methylsulphate, sulphate, phosphate and *p*-toluene-sulphonate. Since the characteristic herbicidal activity of paraquat and diquat salts resides in the paraquat or diquat cation only, it is customary to quote concentrations of active ingredient and rates of application in terms of the amount of paraquat cation or diquat cation used, thus avoiding the inconvenience of having to quote different application rates for different salts of paraquat or diquat. Application rates and concentrations quoted in this specification therefore relate to the amount of paraquat or diquat cation unless otherwise stated.

The rate at which the purine enantiomer is applied to defoliate cotton depends upon a variety of factors, for example the identity of the particular enantiomer chosen for use, but in general a suitable rate is 0.1 to 10, preferably 0.25 to 4, kilograms per hectare. When applied in admixture with paraquat or diquat, the amount of the enantiomer can be correspondingly reduced; usually up to half or more of the weight of the compound can be replaced by the same weight of paraquat or diquat. Thus, instead of using 0.5 kilograms per hectare of the enantiomer a mixture of it and paraquat could be applied, each at a rate of 0.25 kilograms per hectare. An advantage of using these mixtures is that the defoliation is more rapid than when the enantiomer is used alone.

A suitable desiccant is one having the general formula (IV):—



wherein R³ is —OH; —OM wherein M is a cation; phenoxy optionally substituted by at least one halogen or C₁₋₄ alkyl; cycloalkoxy; alkoxy optionally substituted by at least one chlorine, hydroxy, alkoxy, α-(2,5-dichlorophenoxy)propionyloxy, dialkylamino, or phenyl optionally substituted by at least one chlorine, phenoxy or methyl; alkenyloxy; alkylthio optionally substituted by at least one phenyl; alkenylthio; or —NR⁴R⁵ wherein R⁴ is hydrogen, alkoxy, alkyl, alkenyl, phenyl, monoalkylamino or dialkylamino, and R⁵ is hydrogen, alkyl or alkenyl or R⁴ and R⁵, together with the nitrogen atom to which they are attached, form a pyrrolidine or piperidine ring. More details of the use of these compounds as cotton desiccating agents are given in British Patent Application No 9878/77, the disclosure of which

Application is incorporated herein by reference. Another suitable desiccant is the corresponding compound where one or more of the chlorine atoms on the phenyl ring are replaced by fluorine, iodine or lower haloalkyl. More details of these desiccants are given in British Patent Application No. 2024213, the disclosure of which Application is incorporated herein by reference.

The method of the present invention is believed applicable to all species of cultivated cotton, particularly *Gossypium hirsutum* and *barbadense*.

The enantiomers and their salts are believed to show good defoliating activity over a wide range of temperatures; one of the drawbacks of cotton defoliating agents previously used is that, while they may perform quite well at high temperatures in the field, they perform much less well when the temperature falls.

The enantiomers may be used as such for defoliating purposes but are more conveniently formulated into compositions for such usage. The invention provides also a cotton defoliation composition comprising an enantiomer of the invention or a salt thereof, and a carrier or diluent.

The enantiomers can be applied in a number of ways, for example they can be applied formulated or unformulated, directly to the foliage of a plant, or to the medium in which the plant is growing or is to be planted, or they can be sprayed on, dusted on or applied as a cream or paste formulation, or they can be applied as a vapour. Application can be to any part of the plant, for example to the foliage, stems, branches or roots, or to soil surrounding the roots.

The enantiomers are preferably used for defoliating purposes in the form of a composition. The type of composition used in any instance will depend upon the particular purpose envisaged.

The compositions may be in the form of dusting powders or granules comprising the active ingredient a solid diluent or carrier, for example fillers such as kaolin, bentonite, kieselguhr, dolomite, calcium carbonate, talc, powdered magnesia, Fuller's earth, gypsum, Hewitt's earth, diatomaceous earth and China clay. Such granules can be preformed granules suitable for application to the soil without further treatment. These granules can be made either by impregnating pellets of filler with the active ingredient or by pelleting a mixture of the active ingredient and powdered filler.

The compositions may also be in the form of dispersible powders, granules or grains comprising a wetting agent to facilitate the dispersion in liquids of the powder or grains which may contain also fillers and suspending agents.

The aqueous dispersions or emulsions may be prepared by dissolving the active ingredient(s) in an organic solvent optionally containing wetting, dispersing or emulsifying agent(s) and then adding the mixture to water which may also contain wetting, dispersing or emulsifying agent(s). Suitable organic solvents are ethylene dichloride, isopropyl alcohol, propylene glycol, diacetone alcohol, toluene, kerosene, methylnaphthalene, the xylenes, trichloroethylene, furfuryl alcohol, tetrahydrofurfuryl alcohol, and glycol ethers (e.g. 2-ethoxyethanol and 2-butoxyethanol).

The compositions to be used as sprays may also be in the form of aerosols wherein the formulation is held in a container under pressure in the presence of a propellant, e.g. fluorotrichloromethane or dichlorodifluoromethane.

The enantiomers can be mixed in the dry state with a pyrotechnic mixture to form a composition suitable for generating in enclosed spaces a smoke containing the compounds. Alternatively, the enantiomers may be used in microencapsulated form.

By including suitable additives, for example additives for improving the distribution, adhesive power and resistance to rain on treated surfaces, the different compositions can be better adapted for various utilities.

The compositions may also be in the form of liquid preparations for use as dips or sprays which are generally aqueous dispersions or emulsions containing the active ingredient in the presence of one or more surfactants e.g. wetting agent(s), dispersing agent(s), emulsifying agent(s) or suspending agent(s). These agents may be anionic, cationic or non-ionic agents. Suitable cationic agents are quaternary

Suitable anionic agents or soaps, salts of aliphatic monoesters of sulphuric acid (for example sodium lauryl sulphate), and salts of sulphonated aromatic compounds (for example sodium dodecylbenzenesulphonate, sodium, calcium or ammonium lignosulphonate, butylnaphthalene sulphonate, and a mixture of sodium diisopropyl- and triisopropyl-naphthalene sulphonates).

Suitable non-ionic agents are the condensation products of ethylene oxide with fatty alcohols such as oleyl or cetyl alcohol, or with alkyl phenols such as octyl- or nonyl-phenol and octylcresol. Other non-ionic agents are the partial esters derived from long chain fatty acids and hexitol anhydrides, the condensation products of the said partial esters with ethylene oxide, and the lecithins. Suitable suspending agents are hydrophilic colloids (for example polyvinylpyrrolidone and sodium carboxymethylcellulose), and the vegetable gums (for example gum acacia and gum tragacanth).

The compositions for use as aqueous dispersions or emulsions are generally supplied in the form of a concentrate containing a high proportion of the active ingredient(s), the concentrate to be diluted with water before use. These concentrates often should be able to withstand storage for prolonged periods and after such storage be capable of dilution with water in order to form aqueous preparations which remain homogeneous for a sufficient time to enable them to be applied by conventional spray equipment. The concentrates may conveniently contain up to 95%, suitably 10—85%, for example 25—60%, by weight of the active ingredient(s). These concentrates suitably contain organic acids (e.g. alkaryl or aryl sulphonic acids such as xylenesulphonic acid or dodecylbenzenesulphonic acid) since the presence of such acids can increase the solubility of the active ingredient(s) in the polar solvents often used in the concentrates. The concentrates suitably contain also a high proportion of surfactants so that sufficiently stable emulsions in water can be obtained. After dilution to form aqueous preparations, such preparations may contain varying amounts of the active ingredient(s) depending upon the intended purpose, but an aqueous preparation containing 0.0005% or 0.01% to 10% by weight of active ingredient(s) may be used.

The following Examples illustrate the invention; the temperatures are given in degrees Centigrade (°).

EXAMPLE 1

6-Chloropurine (5.0 g) in 1-methylbutylamine (45 mls) was refluxed with stirring for 3 hours. Concentration of the reaction mixture gave a green oil which was dissolved in methylene dichloride, washed with water, dried over magnesium sulphate and concentrated. The oily residue was dissolved in warm cyclohexane and the solution cooled whereupon the product (6.05 g) crystallised. Recrystallisation gave dl-6-(1-Methylbutylamino)-purine (Compound 5) m.p. 132—133°C, which can be resolved in known manner into its enantiomers.

EXAMPLE 2

6-chloropurine (110 g) and DL- α -methylbenzyl amine (236 ml) were dissolved in ethanol (300 mls) and the solution was refluxed for 4½ hours. Solvent was removed and the residue was dissolved in methylene dichloride and the solution washed with water, dried (MgSO₄) and concentrated. Trituration of the residual oil with diethyl ether gave, as a crystalline product, DL-6-(α -methylbenzylamino)purine (141 g), m.p. 196.5—198.5°.

6-chloropurine (5.0 g) and d- α -methylbenzylamine (9.80 g) were dissolved in ethanol (30 mls) and the solution refluxed for 5 hours. Solvent was removed and the residue partitioned between water and methylene dichloride. The organic layer was separated, washed with water and brine, dried (MgSO₄) and concentrated. Trituration of the residual oil with diethyl ether gave a crystalline product which was filtered, washed with more diethyl ether and dried (P₂O₅) at 110° in a vacuum oven to give R-6-(α -methylbenzylamino)purine (7.4 g), m.p. 164.5—166.5°.

The corresponding S-enantiomer (m.p. 165—166.5°) was prepared in a similar fashion except that 1- α -methylbenzylamine was used as one of the starting materials.

EXAMPLE 3

The cotton defoliating activity of the purines was determined in the glass house using the following technique: Cotton plants (cv. Deltapine) obtained from seed sown on 13 October 1978 were treated on 18 January 1979 with test chemical. The test chemicals were formulated in an aqueous medium containing 1% of a surfactant composition (5% Synperonic NPE 1800/Tween 80 in cyclohexanone). Four replicate plants were treated with 35 ml of the aqueous medium. The plants were assessed 7 and 14 days after treatment. The results are shown in Table II.

TABLE II

| Purine | Rate (kg/ha) | No. leaves present at spraying time | % abscission of leaves 7 days after treatment | % abscission of new leaves produced 14 days after treatment | % effect of new growth* |
|---------|--------------|-------------------------------------|-----------------------------------------------|-------------------------------------------------------------|-------------------------|
| 1 | 1 | 9 | 84 | 50 | 31 |
| 1A | 0.2 | 10 | 69 | 8 | 64 |
| | 0.5 | 9 | 84 | 50 | 65 |
| 1B | 1.0 | 9 | 28 | 0 | 99 |
| | 4.0 | 9 | 25 | 0 | 91 |
| Control | | 8 | 9 | 0 | 100 |

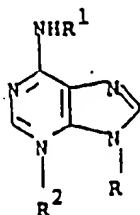
* 100% = No effect

0% = Complete inhibition/killing of new growth

These results show that while Purine 1A is an active cotton defoliant, Purine 1B has only slight activity. Further, Purine 1A at 0.5 kg/ha is as active as Purine 1 at 1.0 kg/ha with respect to defoliation (i.e. it is twice as active) while Purine 1A is more than twice as active as is Purine 1 with respect to inhibition/killing of new growth.

CLAIMS

1. A method of defoliating a growing cotton plant, which method consisting essentially of the step of applying to the plant a cotton defoliating effective amount of an enantiomer of a purine derivative of general formula (I)



wherein R is hydrogen or C₁₋₄ alkyl, R¹ is C₁₋₄ alkyl wherein the carbon atom adjacent to the nitrogen atom is an asymmetric carbon atom or R¹ is α-(C₁₋₄ alkyl)benzyl optionally ring substituted with 1, 2 or 3 substituents selected from the class consisting of halogen, trifluoromethyl and C₁₋₄ alkoxy, and R² is hydrogen or C₁₋₄ alkyl; or a salt thereof with an acid or base, the enantiomer being substantially free from the other enantiomer of the purine derivative.

2. A method as claimed in claim 1 wherein the other enantiomer is associated with less than 5% by weight of said other enantiomer.

3. A method as claimed in claim 2 wherein the enantiomer is R-6-(α-methylbenzylamino)purine.

4. An enantiomer of a purine derivative of general formula (I) defined in claim 1, or a salt thereof, the enantiomer being substantially free from the other enantiomer of the purine derivative.

5. An enantiomer as claimed in claim 4 which is associated with less than 5% by weight of said other enantiomer.

6. An enantiomer according to claim 4 which is R-6-(α-methylbenzylamino) purine.

7. A cotton defoliating composition consisting essentially of a cotton defoliating amount of, as active ingredient, an enantiomer as claimed in any one of claims 4 to 6, or a salt thereof, and a carrier or diluent for the active ingredient.

8. A composition according to claim 7 comprising also paraquat or diquat.